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# Chukvelutilides A–F, phragmalin limonoids from the stem barks of *Chukrasia tabularis* var. *velutina*

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ABSTRACT

Chukvelutilides A–F (**1**–**6**), a new class of C-15-acyl phragmalin type limonoids, featuring a C-16/C-30 δ-lactone ring, were isolated from *Chukrasia tabularis* var. *velutina*. These compounds are suggested to possess a three- or four-carbon enolized acyl substituent at C-15 through a plausible biosynthetic origin. Their structures were elucidated by extensive spectroscopic means, and that of **1** was confirmed by single-crystal X-ray diffraction.



## 1. Introduction

Phragmalins are a type of rings B,D-*seco* limonoids with characteristic A and B-rings of tricycle [3.3.1$^{2,10}$.1$^{1,4}$]decane or tricycle [4.2.1$^{10,30}$.1$^{1,4}$]decane (rearranged phragmalin), most of which exhibit insect antifeeding activity.[1] They have been discovered only from the genera of Meliaceae, such as *Chukrasia*,[1b,2] *Khaya*,[3] *Xylocarpus*,[4] and *Swietenia*.[5] Most of them bear *ortho*-ester group at positions 1,8,9 or 8,9,14 or 8,9,30 or 8,9,11, and C-16/17 δ-lactone ring (ring D), which was in few cases cleavaged, producing C-16/C-17 δ-lactone-*seco* compounds and C-16/C-8 γ-lactone.[1a,2d,4b,5b,6] Among them, nineteen C-15-acyl phragmalin derivatives bearing exclusively a 1,8,9-*ortho*-acetate and C-16/17 δ-lactone ring have been reported,[2a,7] which were suggested to be produced by acyl transfer from a C-30 ester.[1a] In our investigation on the chemical constituents of *Chukrasia tabularis* var. *velutina*, a variety of *Chukrasia tabularis* A. Juss. growing mainly in tropical areas of Asia such as India and southern China,[2e,8] six new C-15-acyl phragmalin derivatives, Chukvelutilides A–F (**1**–**6**), were isolated from the air-dried stem barks of this plant collected in Xishuangbanna, Yunnan Province, China. These novel compounds possess an unprecedented C-16/C-30 δ-lactone ring, a biosynthetically extended three- or four-carbon enolized acyl substituent at C-15, and 1,8,9-*ortho*-acetate group. They are the first examples of C-15-acyl phragmalins with C-16/C-30 δ-lactone ring. We report herein the isolation and structural elucidation of these compounds.

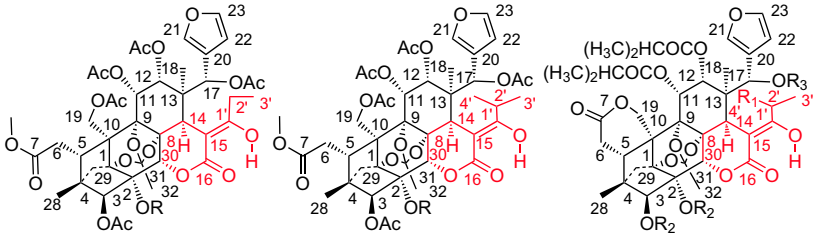


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**Table 1**
$^1$H NMR (500 MHz) and $^{13}$C NMR (125 MHz) data of **1**–**4** (in $CDCl_3$)

| No. | **1** | | **2** | | **3** | | **4** | |
|---|---|---|---|---|---|---|---|---|
| | $\delta_H$ (multi, *J* in Hz) | $\delta_C$ | $\delta_H$ (multi, *J* in Hz) | $\delta_C$ | $\delta_H$ (multi, *J* in Hz) | $\delta_C$ | $\delta_H$ (multi, *J* in Hz) | $\delta_C$ |
| 1 | | 84.4 | | 84.5 | | 84.5 | | 84.6 |
| 2 | | 76.9 | | 83.0 | | 77.0 | | 83.1 |
| 3 | 4.88 (s) | 82.8 | 5.51 (s) | 80.0 | 4.88 (s) | 82.9 | 5.50 (s) | 80.1 |
| 4 | | 45.8 | | 46.4 | | 45.9 | | 46.4 |
| 5 | 3.20 (br d, 10.6) | 36.8 | 3.16 (br d, 10.6) | 36.0 | 3.20 (br d, 9.3) | 36.9 | 3.16 (br d, 9.3) | 36.0 |
| 6a | 2.44 (dd, 16.6, 10.6) | 32.0 | 2.42–2.46 (m)[a] | 32.1 | 2.44 (dd, 17.5, 9.3) | 32.2 | 2.43 (dd, 16.4, 9.3) | 32.1 |
| 6b | 3.22 (br d, 16.6) | | 3.19 (br d, 17.0) | | 3.21 (br d, 17.5) | | 3.18 (br d, 16.4) | |
| 7 | | 173.0 | | 172.9 | | 173.1 | | 173.0 |
| 8 | | 80.3 | | 79.7 | | 80.5 | | 79.8 |
| 9 | | 82.8 | | 82.4 | | 82.9 | | 82.4 |
| 10 | | 47.4 | | 48.2 | | 47.6 | | 48.2 |
| 11 | 6.43 (d, 2.0) | 69.4 | 6.39 (d, 2.0) | 69.4 | 6.42 (d, 2.0) | 69.5 | 6.38 (d, 2.1) | 69.4 |
| 12 | 4.56 (d, 2.0) | 70.4 | 4.56 (d, 2.0) | 70.6 | 4.56 (d, 2.0) | 70.5 | 4.57 (d, 2.1) | 70.6 |
| 13 | | 44.6 | | 44.5 | | 44.4 | | 44.2 |
| 14 | 3.37 (s) | 43.7 | 3.38 (s) | 43.9 | 3.40 (s) | 43.3 | 3.41 (s) | 43.4 |
| 15 | | 92.1 | | 92.3 | | 90.9 | | 91.0 |
| 16 | | 170.0 | | 169.9 | | 170.1 | | 170.3 |
| 17 | 5.91 (s) | 70.1 | 5.95 (s) | 70.2 | 5.90 (s) | 70.1 | 5.95 (s) | 70.1 |
| 18 | 1.44 (s, 3H) | 18.0 | 1.44 (s, 3H) | 18.1 | 1.44 (s, 3H) | 17.8 | 1.44 (s, 3H) | 17.8 |
| 19a | 4.26 (d, 11.7) | 66.0 | 4.25 (d, 11.6) | 66.1 | 4.26 (d, 11.7) | 66.0 | 4.25 (d, 11.6) | 66.1 |
| 19b | 4.55 (d, 11.7) | | 4.54 (d, 11.6) | | 4.55 (d, 11.7) | | 4.54 (d, 11.6) | |
| 20 | | 122.0 | | 122.0 | | 122.1 | | 122.1 |
| 21 | 7.62 (br s) | 141.4 | 7.61 (br s) | 141.4 | 7.62 (br s) | 141.4 | 7.61 (br s) | 141.4 |
| 22 | 6.41 (br s) | 109.8 | 6.39 (br s) | 109.8 | 6.42 (br s) | 109.9 | 6.41 (br s) | 109.8 |
| 23 | 7.28 (t-like, 1.6) | 142.7 | 7.27 (br s) | 142.6 | 7.28 (t-like, 1.6) | 142.8 | 7.28 (t-like, 1.6) | 142.7 |
| 28 | 0.99 (s, 3H) | 14.4 | 1.00 (s, 3H) | 14.6 | 0.99 (s, 3H) | 14.4 | 1.00 (s, 3H) | 14.5 |
| $29_{pro\text{-}R}$ | 1.91 (s, 2H) | 39.6 | 1.86 (d, 11.8) | 40.2 | 1.92 (s, 2H) | 39.7 | 1.86 (d, 11.9) | 40.2 |
| $29_{pro\text{-}S}$ | | | 1.96 (d, 11.8) | | | | 1.97 (d, 11.9) | |
| 30 | 5.51 (s) | 73.7 | 5.75 (s) | 73.6 | 5.49 (s) | 73.7 | 5.74 (s) | 73.6 |
| 31 | | 119.9 | | 119.8 | | 120.0 | | 119.8 |
| 32 | 1.64 (s, 3H) | 20.8 | 1.63 (s, 3H) | 20.8 | 1.63 (s, 3H) | 20.9 | 1.62 (s, 3H) | 20.8 |
| 1′ | | 179. 9 | | 179.8 | | 183.3 | | 183.2 |
| 2′ | 2.41, 2.57 (m, 2H) | 25.7 | 2.42, 2.56 (m, 2H)[a] | 25.7 | 2.98 (m) | 30.3 | 2.98 (m) | 30.2 |
| 3′ | 1.25 (t, 7.5, 3H) | 11.2 | 1.27 (t, 7.4, 3H) | 11.0 | 1.17 (d, 6.9) | 20.4 | 1.20 (d, 6.8) | 20.2 |
| 4′ | | | | | 1.32 (d, 6.6) | 18.4 | 1.32 (d, 6.6) | 18.4 |
| 1′-OH | 13.58 (s) | | 13.69 (s) | | 13.74 (s) | | 13.84 (s) | |
| 7-OMe | 3.73 (s, 3H) | 52.0 | 3.71 (s, 3H) | 52.0 | 3.73 (s, 3H) | 52.0 | 3.71 (s, 3H) | 51.9 |
| 2-OAc | | | | 169.2 | | | | 169.4 |
| | | | 2.09 (s, 3H) | 21.8 | | | 2.10 (s, 3H) | 21.8 |
| 3-OAc | | 170.3 | | 169.9 | | 170.3 | | 170.0 |
| | 2.36 (s, 3H) | 20.8 | 2.38 (s, 3H) | 21.0 | 2.36 (s, 3H) | 20.7 | 2.38 (s, 3H) | 20.9 |
| 11-OAc | | 168.9 | | 168.8 | | 168.9 | | 168.8 |
| | 2.12 (s, 3H) | 21.0 | 2.12 (s, 3H) | 21.2 | 2.12 (s, 3H) | 20.9 | 2.12 (s, 3H) | 20.7 |
| 12-OAc | | 169.0 | | 168.9 | | 169.0 | | 169.9 |
| | 1.58 (s, 3H) | 19.7 | 1.57 (s, 3H) | 19.7 | 1.58 (s, 3H) | 19.7 | 1.58 (s, 3H) | 19.6 |
| 17-OAc | | 168.9 | | 168.6 | | 168.9 | | 168.7 |
| | 1.97 (s, 3H) | 20.7 | 1.95 (s, 3H) | 20.7 | 1.96 (s, 3H) | 20.4 | 1.94 (s, 3H) | 20.4 |
| 19-OAc | | 171.0 | | 170.9 | | 171.1 | | 171.0 |
| | 2.07 (s, 3H) | 20.8 | 2.07 (s, 3H) | 21.0 | 2.07 (s, 3H) | 21.1 | 2.07 (s,3H) | 21.0 |

[a] Signal pattern unclear due to overlapping.

## 2. Result and discussion

Chukvelutilide A (**1**), colorless crystals, has a molecular formula of $C_{42}H_{50}O_{20}$ as determined by the HRESIMS ion at *m*/*z* 873.2835 $[M-H]^-$ (calcd: 873.2822), which indicated 18 degrees of unsaturation. The IR absorption bands at 3447, 1748, 1646, and 1611 $cm^{-1}$ suggested the presence of hydroxyl, ester, and β-dicarbonyl groups. Its UV spectrum $\lambda_{max}$ (MeOH) 209 (3.17), 268 (3.36) nm was characteristic of a typical furanyl[9] and a β-dicarbonyl chromophore.[2a] The $^1$H and $^{13}$C NMR data of **1** (Table 1) indicated that ten of the eighteen units of unsaturation were present as three carbon–carbon double bonds and seven carbonyl ester groups. Therefore, the remaining degrees of unsaturation were accounted for by the octacyclic core. The data from decouplings and the subsequent 2D NMR studies (HMBC and HSQC) suggested that **1** was a phragmalin limonoid. The down-field shifted proton resonances at $\delta_H$ 7.62 (br s, H-21), 6.41 (br s, H-22), and 7.28 (t-like, *J*=1.6, H-23) were typical of a β-substituted furanyl moiety. Two overlapped protons at $\delta_H$ 1.91 correlating in the HSQC spectrum to a methylene signal at $\delta_C$ 39.6 were indicative of the equivalent H-29 protons of the 4, 29, 1-ring-bridge,[1b] which was confirmed by HMBC (Fig. 1) correlations

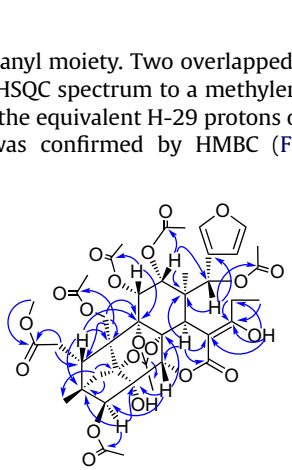


**Figure 1.** Key HMBC correlations (→) of **1**.

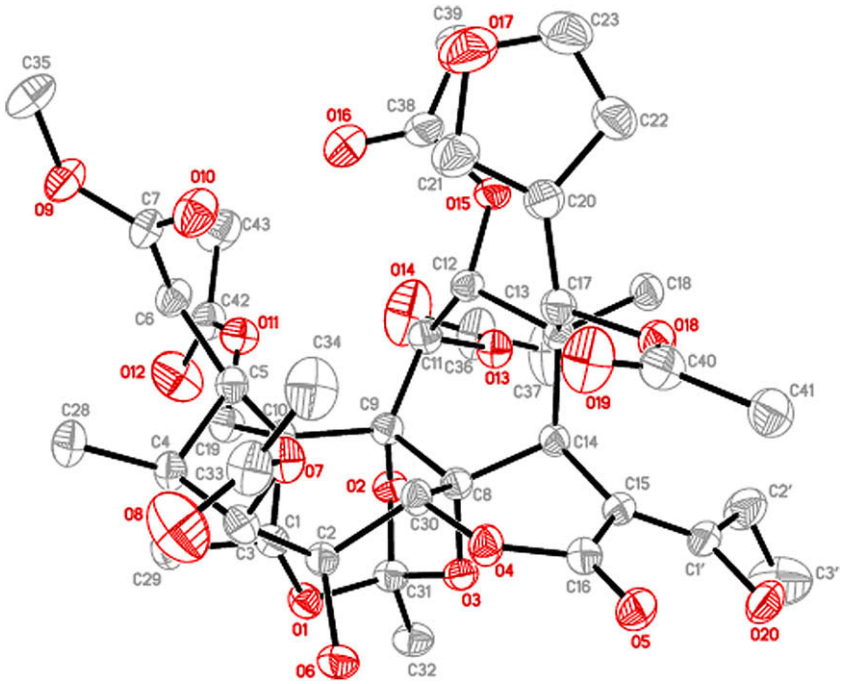



**Figure 2.** X-ray crystallographic structure of **1**.

observed from the H-29 methylene protons to the tertiary methyl signal at $\delta_C$ 14.4 (C-28) and the quaternary carbons at $\delta_C$ 84.4 (C-1) and 45.8 (C-4). The signals attributable to an ABX-coupling system were observed at $\delta_H$ 2.44 (dd, $J$=10.6, 16.6 Hz, Ha-6), 3.22 (br d, $J$=16.6 Hz, Hb-6), and 3.20 (br d, $J$=10.6 Hz, H-5). An HMBC correlation between H-6 signal and a carbomethoxy signal at $\delta_C$ 173.0 confirmed this as C-7, with the accompanying methyl ester resonances at $\delta_H$ 3.73 (3H, s) and $\delta_C$ 52.0 (O–Me), and also the C-6–C-7 appendage. A singlet proton signal at $\delta_H$ 5.91 was assignable to H-17 by correlations observed in the HMBC spectrum with the quaternary carbon at $\delta_C$ 122.0 (C-20) of the furan ring along with C-12 ($\delta_C$ 70.4), C-13 ($\delta_C$ 44.6), the C-18 methyl carbon at $\delta_C$ 18.0, and an acetyl carbon at $\delta_C$ 168.9. A down-field shifted singlet methine proton at $\delta_H$ 5.51, assigned to H-30 showed significant HMBC correlations with four quaternary carbons at $\delta_C$ 76.9, 80.3, 43.7, and 82.8 to be assigned to C-2, C-8, C-14, and the methine carbon of C-3. Two oxygenated methylene signals at $\delta_H$ 4.26 and 4.55 (d, $J$=11.7 Hz) due to protons attached to a carbon at $\delta_C$ 66.0 were attributable to C-19 by the observed HMBC correlations with carbons at $\delta_C$ 47.4 (C-10), 82.8 (C-9), 36.8 (C-5), and 171.0 (C-19-CO), which suggested that the 19-methyl had been acetoxylated.[1b,10]

The presence of a characteristic enolic proton signal at $\delta_H$ 13.58, and the β-ketolactone carbon signals at $\delta_C$ 179.9 (C-1′), 92.1 (C-15), and 170.0 (C-16) and the HMBC correlations of β-ketolactone carbon signals with H-14 ($\delta_H$ 3.37) indicated that **1** was a C-15-acyl phragmalin limonoid derivative.[2a,7e] In the HMBC spectrum of **1**, the observed correlations of ethyl signals at $\delta_H$ 2.41, 2.57 (2H, m, H-2′), and 1.25 (3H, t, $J$=7.5 Hz, H-3′) with the carbon signal at $\delta_C$ 179.9 (C-1′) suggested a propionyl at C-15. A quaternary carbon at $\delta_C$ 119.9 (C-31) showing a HMBC correlation with a singlet methyl signal at $\delta_H$ 1.64 (H-32) suggested the presence of an *ortho*-acetate group, the positions of which remained to be determined as 2D NMR spectra did not provide sufficient information to elucidate the pattern of connection of these quaternary carbons. The remaining one degree of unsaturation suggested that an additional ring was required. Previously isolated this type of compounds were exclusively of C-16/C-17 δ-lactone ring, which was excluded for **1** due to the observed HMBC correlation between H-17 and an acetate carbon at $\delta_C$ 168.9. However, the site of lactonization could not be determined directly by the HMBC spectrum for no protons correlated with the carbonyl at $\delta_C$ 170.0 (C-16). Fortunately, a single-crystal X-ray diffraction (Fig. 2) was performed and enabled us to

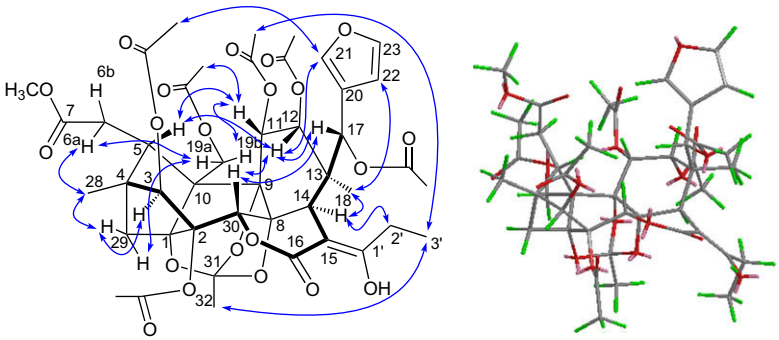



**Figure 3.** Key NOESY correlations (↔) and the 3D computer modeling of **2**.

**Table 2**
$^1$H NMR (500 MHz) and $^{13}$C NMR (125 MHz) data of **5** and **6** (in $CDCl_3$)

| No. | **5** | | **6** | |
|---|---|---|---|---|
| | $\delta_H$ (multi, $J$ in Hz) | $\delta_C$ | $\delta_H$ (multi, $J$ in Hz) | $\delta_C$ |
| 1 | | 84.9 | | 85.3 |
| 2 | | 82.8 | | 77.8 |
| 3 | 5.50 (s) | 80.9 | 3.76 (s) | 83.3 |
| 4 | | 46.8 | | 46.4 |
| 5 | 2.66 (m)[a] | 34.6 | 2.79 (br s) | 33.5 |
| 6a | 2.66 (m)[a] | 30.8 | 2.63 (m)[a] | 30.9 |
| 6b | 3.04 (dd, 18.0, 5.3) | | 2.98 (dd, 16.8, 4.8) | |
| 7 | | 171.7 | | 172.6 |
| 8 | | 79.1 | | 80.2 |
| 9 | | 82.5 | | 83.1 |
| 10 | | 45.6 | | 45.0 |
| 11 | 5.48 (d, 2.3) | 68.6 | 5.47 (d, 1.9) | 69.0 |
| 12 | 4.77 (d, 2.3) | 69.3 | 4.81 (d, 1.9) | 68.9 |
| 13 | | 44.9 | | 45.0 |
| 14 | 3.25 (s) | 44.2 | 3.26 (s) | 43.7 |
| 15 | | 92.0 | | 90.6 |
| 16 | | 169.7 | | 170.6 |
| 17 | 5.83 (s) | 69.9 | 5.86 (s) | 69.2 |
| 18 | 1.59 (s, 3H) | 17.9 | 1.59 (s, 3H) | 18.1 |
| 19a | 4.69 (d, 14.0) | 67.9 | 4.65 (d, 14.0) | 67.9 |
| 19b | 4.72 (d, 14.0) | | 4.70 (d, 14.0) | |
| 20 | | 122.1 | | 121.6 |
| 21 | 7.33 (br s) | 140.7 | 7.41 (br s) | 141.7 |
| 22 | 6.29 (d, 1.0) | 110.0 | 6.29 (br s) | 109.8 |
| 23 | 7.31 (t-like, 1.5) | 143.1 | 7.27 (br s) | 143.0 |
| 28 | 1.12 (s, 3H) | 14.3 | 1.15 (s, 3H) | 14.2 |
| $29_{pro\text{-}R}$ | 1.85 (d, 11.6) | 39.3 | 1.74 (d, 11.1) | 38.4 |
| $29_{pro\text{-}S}$ | 2.45 (d, 11.6) | | 2.27 (d, 11.1) | |
| 30 | 5.42 (s) | 73.5 | 5.36 (s) | 73.2 |
| 31 | | 119.6 | | 119.7 |
| 32 | 1.61 (s, 3H) | 20.6 | 1.60 (s, 3H) | 20.7 |
| 1′ | | 180.4 | | 183.8 |
| 2′ | 2.40, 2.58 (m, 2H) | 25.6 | 3.00 (m)[a] | 30.3 |
| 3′ | 1.25 (m, 3H)[a] | 11.1 | 1.13 (d, 6.8, 3H) | 20.3 |
| 4′ | | | 1.27 (d, 6.5, 3H) | 18.2 |
| 1′-OH | 13.69 (s) | | 13.68 (s) | |
| 2-OAc | | 169.3 | | |
| | 2.10 (s, 3H) | 21.6 | | |
| 3-OAc | | 169.3 | | |
| | 2.32 (s, 3H) | 21.1 | | |
| 11-OCOCHMe$_2$ | | 175.1 | | 175.1 |
| | 2.66 (m)[a] | 34.2 | 2.68 (m)[a] | 34.2 |
| | 1.21 (d, 6.9, 3H) | 18.6 | 1.20 (d, 6.9, 3H) | 18.5 |
| | 1.24 (m, 3H)[a] | 19.3 | 1.24 (d, 7.1, 3H) | 19.4 |
| 12-OCOCHMe$_2$ | | 175.3 | | 175.1 |
| | 2.16 (m)[a] | 33.4 | 2.20 (m) | 33.5 |
| | 0.91 (d, 6.9, 3H) | 17.7 | 0.95 (d, 6.9, 3H) | 17.8 |
| | 0.94 (d, 7.1, 3H) | 18.8 | 0.98 (d, 7.1, 3H) | 18.9 |
| 17-OAc | | 168.6 | | |
| | 1.93 (s, 3H) | 20.6 | | |
| 17-OCOCHMe$_2$ | | | | 174.9 |
| | | | 2.43 (m) | 34.0 |
| | | | 1.07 (d, 7.2, 3H) | 18.1 |
| | | | 1.07 (d, 7.2, 3H) | 19.0 |

[a] Signal pattern unclear due to overlapping.

resolve these uncertainties and thus demonstrated the structure of **1** as depicted, which possess a 1,8,9-*ortho*-acetate and an unprecedented six-membered C-16/C-30 δ-lactone ring.

The molecular formula of Chukvelutilide B (**2**), $C_{44}H_{52}O_{21}$, was determined by the HRESIMS ion at $m/z$ 915.2912 $[M-H]^-$ (calcd: 915.2928). Analysis of the $^1$H and $^{13}$C NMR data of **2** showed that it was likely an acetyl derivative of **1**, and this was supported by 42 mass units more in the molecular formula of **2** than that of **1**. The C-2 signal at $\delta_C$ 76.9 and H-3 signal at $\delta_H$ 4.88 of **1** down-field shifted severely to $\delta_C$ 83.0 and $\delta_H$ 5.11 of **2** (Table 1), suggesting the substitution of a 2-OAc in **2**. Interestingly, the overlapped methylene proton signals (2H-29) of **1** were separated into two signals at $\delta_H$ 1.86 (d, $J$=11.8, $H_{pro\text{-}R}$-29) and 1.96 (d, $J$=11.8, $H_{pro\text{-}S}$-29) of **2**, which could be attributed to an anisotropic effect due to the carbonyl of the 2-OAc. NOESY experiment (Fig. 3) was conducted using a molecular model in order to elucidate the stereochemistry of **2**. Strong cross-peaks of the H-12 signal at $\delta_H$ 4.56 with protons at $\delta_H$ 3.16 (H-5), 5.95 (H-17), and 5.75 (H-30), and of H-30 with H-17 indicated a β-orientation for these four protons and the folded conformation of **2**. The β-orientation of H-17 was also suggested by the high field shift of the acetyl groups at C-12 to $\delta_H$ 1.57 caused by an anisotropic effect of the furan ring located on the same side of the molecule. NOESY correlations of H-14 with Me-18, and of H-11 with H-5 and an oxymethene signal at $\delta_H$ 4.54 (Hb-19), revealed the stereochemistry of the protons at these positions to be H-14α and H-11β, respectively. The correlation of H-30 with H-12 and H-17 also clarified the ring C to be a skew boat form. The 29-methylene proton signals at $\delta_H$ 1.86 ($H_{pro\text{-}R}$-29) showed NOE correlations with the H-3 and Me-28 proton signals helped to establish 3α-H, which also confirmed by the observation of a NOE correlation of the 3-OAc signal with H-21 of the furan ring. The correlation of H-3′ with 11-OAc and Me-32 suggested that the *ortho*-acetate unit was fused in the α-orientation. The relative configuration of **2** was thus established to be the same as those of **1**, resolved by a single-crystal X-ray diffraction.

Chukvelutilides C (**3**) and D (**4**) with molecular formulas of $C_{43}H_{52}O_{20}$ (at $m/z$ 887.2954 $M-H]^-$) and $C_{45}H_{54}O_{21}$ (at $m/z$ 929.3050 $M-H]^-$) as determined by HREIMS showed the presence of one more $CH_2$ unit than those of **1** and **2**, respectively. The only difference was the replacement of the ethyl group at C-1′ in **1** and **2** by a isopropyl group in **3** and **4**, which was demonstrated by the observed correlations of the isopropyl proton signals with the enolic carbon signals in their HMBC spectrum. Thus, the structures of chukvelutilides C (**3**) and D (**4**) were established as the respective analogues of **1** and **2** by incorporating a biosynthetically extended C4 unit into C-15 instead of a C3 one.

Chukvelutilide E (**5**) was isolated as white amorphous powder with the molecular formula $C_{45}H_{54}O_{19}$ as determined by the HRESIMS ion at $m/z$ 897.3167 $[M-H]^-$ (calcd: 897.3186). The IR absorption bands at 3450, 1755, 1647, and 1607 cm$^{-1}$ implied the presence of hydroxyl, ester, and β-dicarbonyl groups. From the $^1$H and $^{13}$C NMR data of **5** (Table 2), the presence of three acetoxyls, two isobutyryls, a β-substituted furanyl ring, and an *ortho*-acetate was recognized. The data from decouplings and the subsequent 2D NMR studies (HMBC, HSQC, and NOESY) suggested that **5** was also a phragmalin limonoid with the same basic skeleton as **1**. In the HMBC spectrum of **5** (Fig. 4), two germinal oxygenated methylene signals at $\delta_H$ 4.69 and 4.72 (each d, $J$=11.7) corresponded to a carbon at $\delta_C$ 67.9 (C-19) showed correlations with carbons at $\delta_C$ 45.6 (C-10), 82.5 (C-9), 34.6 (C-5), and 171.1 (C-7), which suggested that the 19-methyl had been oxygenated and formed a six-membered lactone ring with a lactonic carbonyl (C-7).[1b,3e] The characteristic enolic proton signal at $\delta_H$ 13.69 and carbon signals at $\delta_C$ 180.4 (C-1′), 92.0 (C-15), and 169.7 (C-16) indicated that **5** was a C-15-acyl phragmalin limonoid derivative. In the HMBC spectrum of **5**, the observed correlations of an ethyl signal [$\delta_H$ 2.40 and 2.58 (2H, m, H-2′), 1.25 (3H, m, H-3′); $\delta_C$ 25.6 (C-2′) and 11.1 (C-3′)] with the

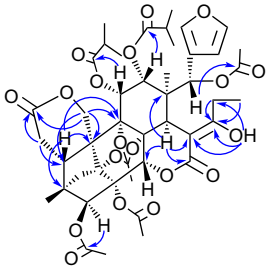


**Figure 4.** Selected HMBC (→) correlations of **5**.

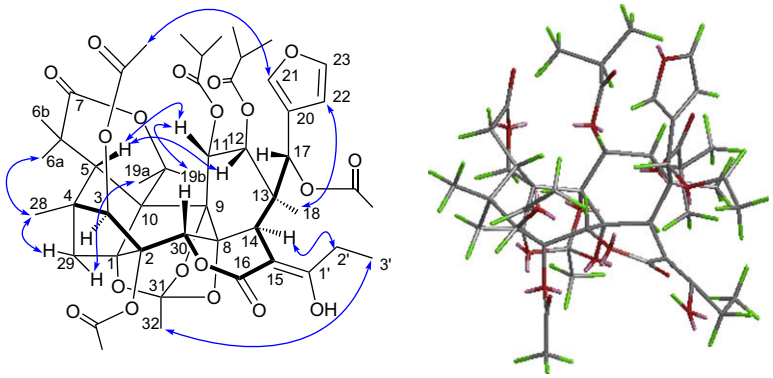
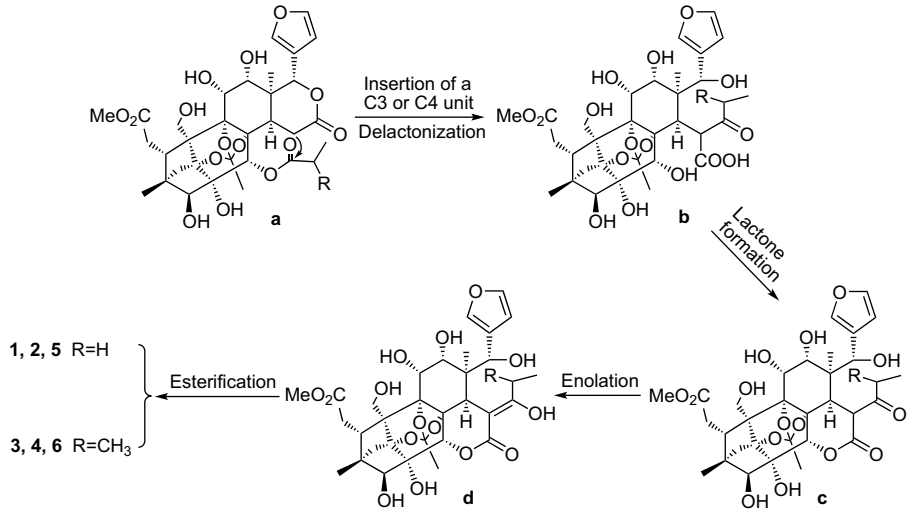


**Figure 5.** Selected NOESY correlations (↔) and the 3D computer modeling of **5**.




**Scheme 1.** The plausible biosynthetic origin of **1**–**6**.

enolic carbon signal at $\delta_C$ 180.4(C-1′) suggested a propionyl at C-15 of **5** like that of **1** and **2**. Furthermore, the locations of the three acetoxyls and two isobutyryls at C-2 ($\delta_C$ 82.8), C-3 ($\delta_C$ 80.9), C-17 ($\delta_C$ 69.9), C-11 ($\delta_C$ 68.6), and C-12 ($\delta_C$ 69.3), respectively, were determined by HMBC cross-peaks from the corresponding protons to the carbonyl carbons. The stereochemistry of **5** was elucidated by the NOE correlations (Fig. 5) and indicated that all of the asymmetric carbons had the same configurations as those of **2**. The structure of **5** was thus established as shown.

Chukvelutilide F (**6**), white amorphous power, has the molecular formula $C_{44}H_{56}O_{17}$, determined by the HRESIMS ion at *m*/*z* 855.3413 $[M-H]^-$ (calcd: 855.3444). The IR absorption bands at 3444, 1743, 1641, and 1602 $cm^{-1}$ suggested the presence of hydroxyl, ester, and β-dicarbonyl groups. The NMR data of **6** (Table 2) exhibited the signals of three isobutyryls, a β-substituted furanyl ring, and an *ortho*-acetate. Analysis of $^1H$ and $^{13}C$ NMR data (Table 2) of **6** indicated that it was also a C-15-acyl phragmalin limonoid with C-7/C-19, C-16/C-30 δ-lactones and 1,8,9-*ortho*-acetate like **5**, and incorporated a biosynthetically extended C4 unit into C-15 the same as **3** and **4**. Three isobutyryloxyl groups were assignable to C-11 ($\delta_C$ 69.0), C-12 ($\delta_C$ 68.9), and C-17 ($\delta_C$ 69.2) on the basis of their corresponding HMBC correlations. The structure of **6** was thus established, and its relative configuration was determined to be the same as **2** by the NOESY spectrum.

The biosynthetic origin of **1**–**6** (Scheme 1) was proposed to be the phragmalin type limonoid (**a**)[1b] with propionyl or isobutyryl unit at C-30.[1a] Insertion of a propionyl or isobutyryl unit from C-30 through a Claisen reaction[2c] and meanwhile the cleavage of C-16/C-17 δ-lactone, would produce a key intermediate (**b**), then annelated to yield an intermediate (**c**) with C-16/C-30 δ-lactone ring, which is prone to be in enolic form (**d**) due to two adjacent carbonyl groups. Further esterification of it (**d**) would give **1**–**6**, respectively.

## 3. Experimental section

### 3.1. General experimental procedures

Melting point was measured on an XT-4 micromelting point apparatus, uncorrected. Optical rotations were measured with a JASCO P-1020 polarimeter, CD spectra were obtained on a JASCO 810 spectropolarimeter, and UV spectra were recorded quantitatively on a Shimadzu UV-2501 PC spectrophotometer. IR (KBr-disks) spectra were recorded by Bruker Tensor 27 spectrometer. NMR spectra were recorded on Bruker ACF-500 NMR instrument ($^1H$: 500 MHz, $^{13}C$: 125 MHz) with TMS as internal standard. Mass spectra were obtained on a MS Agilent 1100 Series LC/MSD Trap mass spectrometer (ESI-MS) and a Micro Q-TOF MS (HRESIMS), respectively. All solvents used were of analytical grade (Jiangsu Hanbang Sci. & Tech. Co. Ltd). Silica gel (Qingdao Haiyang Chemical Co. Ltd), Sephadex LH-20 (Pharmacia), and RP-$C_{18}$ (40–63 μm, FuJi) were used for column chromatography. Preparative HPLC was carried out using Agilent 1100 Series with Shim-park RP-$C_{18}$ column (20×200 mm) and 1100 Series Multiple Wavelength detector.

### 3.2. Plant material

The air-dried stem barks of *C. tabularis* var. *velutina* were collected from Xishuangbanna, Yunnan Province, China, and were authenticated by Professor Mian Zhang of Research Department of Pharmacognosy, China Pharmaceutical University. A voucher specimen (No. 2006-MML) has been deposited in the Department of Natural Medicinal Chemistry, China Pharmaceutical University.

### 3.3. Extraction and isolation

The air-dried stem barks (10 kg) were extracted with refluxing 95% ethanol three times. The EtOH extract was concentrated under reduced pressure (2000 g) and then extracted with $CHCl_3$ to give the chloroform extract (300 g). The oily chloroform extract was dissolved in 2 L 50% MeOH and $H_2O$ and then extracted with petroleum ether (PE). After removal of the fatty components, 210 g of extraction was obtained, which was subjected to a silica gel column eluted with gradient $CHCl_3$/MeOH (1:0 to 1:2) to afford eight fractions (Fr. A–H) according to TLC monitor. Fr. C (22 g) was chromatographed on a column of silica gel eluted successively with a gradient of PE/EtOAc (4:1 to 1:2) to give eight sub-fractions (Fr. C1–C8). Fr. C4 was chromatographed on a column of reversed-phase $C_{18}$ silica gel eluted with MeOH/$H_2O$ (5:5 to 7:3) to give three sub-fractions (Fr. C4a–C4c), then Fr. C4a was separated by preparative HPLC using MeOH/$H_2O$ (68:32, 10 mL/min) as the mobile phase to give **1** (15 mg) and **2** (20 mg). Fr. C3 was chromatographed on a column of reversed-phase $C_{18}$ silica gel eluted with MeOH/$H_2O$ (1:1 to 3:1) to give four sub-fractions (Fr. C3a–C3d), then Fr. C3c was separated by preparative HPLC using MeOH/$H_2O$ (68:32, 10 mL/min) as the mobile phase to give **3** (5 mg) and **4** (6 mg). Fr. B (20 g) was chromatographed on a column of silica gel eluted successively with a gradient of PE/EtOAc (6:1 to 1:2) to give seven sub-fractions (Fr. B1–B7). Fr. B3 was chromatographed on a column of reversed-phase $C_{18}$ silica gel eluted with MeOH/$H_2O$ (5:5 to 7:3) to give five sub-fractions (Fr. B3a–B3e), then Fr. B3e was separated by preparative HPLC using MeOH/$H_2O$ (71:29, 10 mL/min) as the mobile phase to give **5** (5 mg). Fr. D (30 g) was chromatographed on a column of silica gel eluted successively with a gradient of PE/EtOAc (5:2 to 1:2) to give seven sub-fractions (Fr. D1–D7). Fr. D2 was chromatographed on a column of reversed-phase $C_{18}$ silica gel eluted with MeOH/$H_2O$ (2:3 to 3:1) to give four sub-fractions (Fr. D2a–D2d). Fr. D2b was chromatographed on a column of Sephadex LH-20 eluted with $CHCl_3$/MeOH (1:1) to give a major band, and from which compound **6** (6 mg) was obtained by recrystallization.

#### 3.3.1. *Chukvelutilide A (**1**)*

Colorless crystals (MeOH/$H_2O$); mp 308–310 °C; $[\alpha]_D^{25}$ −51.3 (*c* 0.133, $CH_3OH$); UV ($CH_3OH$) $\lambda_{max}$ (log $\varepsilon$) 209 (3.17), 268 (3.36) nm; CD ($CH_3OH$, $\Delta\varepsilon$) 206 (−1.629), 222 (+0.450), 265 (−3.521) nm; IR (KBr) $\nu_{max}$ 3447, 2970, 1748, 1646, 1611, 1371, 1224 $cm^{-1}$; $^1H$ NMR and $^{13}C$ NMR data, see Table 1; negative ESIMS *m*/*z* (rel int): 873.4 $[M-H]^-$ (100); HRESIMS *m*/*z*: 873.2835 $[M-H]^-$ (calcd for $C_{42}H_{49}O_{20}$: 873.2822).

#### 3.3.2. *Chukvelutilide B (**2**)*

White amorphous power; $[\alpha]_D^{25}$ −54.9 (*c* 0.105, $CH_3OH$); UV ($CH_3OH$) $\lambda_{max}$ (log $\varepsilon$) 206 (3.17), 268 (3.30) nm; CD ($CH_3OH$, $\Delta\varepsilon$) 206 (−3.481), 239 (−0.024), 268 (−2.425) nm; IR (KBr) $\nu_{max}$ 3460, 2975, 1747, 1644, 1608, 1371, 1224 $cm^{-1}$; $^1H$ NMR and $^{13}C$ NMR data, see Table 1; negative ESIMS *m*/*z* (rel int): 915.5 $[M-H]^-$ (100); HRESIMS *m*/*z*: 915.2912 $[M-H]^-$ (calcd for $C_{44}H_{51}O_{21}$: 915.2928).

#### 3.3.3. *Chukvelutilide C (**3**)*

White amorphous power; $[\alpha]_D^{25}$ −52.8 (*c* 0.095, $CH_3OH$); UV ($CH_3OH$) $\lambda_{max}$ (log $\varepsilon$) 208 (3.17), 268 (3.36) nm; CD ($CH_3OH$, $\Delta\varepsilon$) 206 (−1.556), 221 (+0.126), 267 (−1.937) nm; IR (KBr) $\nu_{max}$ 3476, 2971, 1748, 1644, 1605, 1372, 1227 $cm^{-1}$; $^1H$ NMR and $^{13}C$ NMR data, see Table 1; negative ESIMS *m*/*z* (rel int): 887.4 $[M-H]^-$ (100); HRESIMS *m*/*z*: 887.2954 $[M-H]^-$ (calcd for $C_{43}H_{51}O_{20}$: 887.2979).

#### 3.3.4. *Chukvelutilide D (**4**)*

White amorphous power; $[\alpha]_D^{25}$ −36.8 (*c* 0.100, $CH_3OH$); UV ($CH_3OH$) $\lambda_{max}$ (log $\varepsilon$) 208 (3.17), 268 (3.31) nm; CD ($CH_3OH$, $\Delta\varepsilon$) 208 (−3.252), 241 (+0.215), 266 (−1.288) nm; IR (KBr) $\nu_{max}$ 3459, 2970, 1751, 1646, 1606, 1371, 1225 $cm^{-1}$; $^1H$ NMR and $^{13}C$ NMR data, see Table 1; negative ESIMS *m*/*z* (rel int): 929.6 $[M-H]^-$ (100); HRESIMS *m*/*z*: 929.3050 $[M-H]^-$ (calcd for $C_{45}H_{53}O_{21}$: 929.3084).

#### 3.3.5. *Chukvelutilide E (**5**)*

White amorphous power; $[\alpha]_D^{25}$ −6.8 (*c* 0.085, $CH_3OH$); UV ($CH_3OH$) $\lambda_{max}$ (log $\varepsilon$) 204 (3.16), 268 (3.36) nm; CD ($CH_3OH$, $\Delta\varepsilon$) 210 (−3.539), 243 (+0.538), 264 (−0.811) nm; IR (KBr) $\nu_{max}$ 3450, 2978, 1755, 1647, 1607, 1373, 1221 $cm^{-1}$; $^1H$ NMR and $^{13}C$ NMR data, see Table 2; negative ESIMS *m*/*z* (rel int): 897.4 $[M-H]^-$ (100); HRESIMS *m*/*z*: 897.3167 $[M-H]^-$ (calcd for $C_{45}H_{53}O_{19}$: 897.3186).

#### 3.3.6. *Chukvelutilide F (**6**)*

White amorphous power; $[\alpha]_D^{25}$ −5.4 (*c* 0.100, $CH_3OH$); UV ($CH_3OH$) $\lambda_{max}$ (log $\varepsilon$) 205 (3.16), 268 (3.36) nm; CD ($CH_3OH$, $\Delta\varepsilon$) 213 (−1.918), 240 (+0.137), 266 (−0.931) nm; IR (KBr) $\nu_{max}$ 3444, 2976, 1743, 1641, 1602, 1243, 1147 $cm^{-1}$; $^1H$ NMR and $^{13}C$ NMR data, see Table 2; negative ESIMS *m*/*z* (rel int): 855.6 $[M-H]^-$ (100); HRESIMS *m*/*z*: 855.3413 $[M-H]^-$ (calcd for $C_{44}H_{55}O_{17}$: 855.3444).

### 3.4. X-ray crystallographic analysis of 1

Colorless crystals of **1** were obtained in the mixture of solvents MeOH/$H_2O$. Crystal data were obtained on a Bruker Smart-1000 CCD with a graphite monochromator, Mo Kα radiation ($\lambda$=0.71073 Å) at 298(2) K. The crystal structure was solved by direct methods using SHELX-97 (Sheldrick, G. M. University of Göttingen: Göttingen, Germany, 1997) and expanded using difference Fourier techniques, refined by SHELX-97 (Sheldrick, G. M., 1997). Crystallographic data for the structure of **1** have been deposited in the Cambridge Crystallographic Data Centre with the deposition number of CCDC 698929.

#### 3.4.1. *X-ray data of **1***

$C_{42.25}H_{51}O_{20.25}$ ($C_{42}H_{50}O_{20}\cdot 1/4CH_3OH$), *M*=882.83, monoclinic, dimensions: 0.28×0.17×0.11 mm, *d*=1.350 g/$cm^3$, space group *P*2(1)2(1)2(1), *Z*=4, *a*=10.8609(10), *b*=17.267(2), *c*=23.154(3) Å, $\alpha=\beta=\gamma=90°$, *V*=4342.3(9) $Å^3$, reflections collected/unique: 17,942/4267 ($R_{int}$=0.0589), number of observation [$I>2\sigma(I)$] 4267, parameters 577, final *R* indices [$I>2\sigma(I)$]: $R_1$=0.0559, $wR_2$=0.1427.

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### Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.046.

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